The disclosures of both Bowen and Gopinath have been described in prior papers.

The Examiner relies on Bowen for teaching "that simultaneous quantitation of SALS and fluorescent labeled monoclonal antibody binding to CD45, CD16, and CD11b define highly reproducible developmental maturation patterns of the granulocytic cell population series in flow cytometry." (Office Action, pages 4-5).

The Examiner admits Bowen does not teach or disclose "distinguishhing eosinophils and neutrophilic cells in the granulocytic cells measured in step 4) of claim 1 on the basis of the intensity of fluorescence from the first fluorescence-labeled antibody and the intensity of fluorescence from the second or third fluorescence-labeled antibody, as recited in step 5) in claim 1" (Office Action, page 5). The Examiner also admits that Bowen does not teach or disclose staining leucocytes after the erythrocytes are removed from the hematological sample.

Applicants respectfully point out that if, as the Examiner admits, step 5) of claim 1 is not disclosed or taught by Bowen, this citation cannot also disclose step 6), which uses cells classified in step 5). Nonetheless, the Examiner bridges the acknowledged gap only as to step 5) by referencing Gopinath, which the Examiner regards as teaching "the most accurate isolation of eosinophils from neutrophils [being] obtained by a combination of side angle scatter and anti-CD 16 PE fluorescence intensity" (Office Action, page 5).

The Examiner then concludes that it would have been obvious to one of ordinary skill in the art to incorporate the teaching of Gopinath in:

> "...distinguishing between neutrophils and eosinophil populations, with the flow cytometric method as taught by Bowen because Gopinath specifically taught that CD 16 fluorescence negativity in addition to side angle scatter measurement provides for accurate isolation of eosinophils from neutrophils in granulocytic populations and Bowen specifically taught obtaining fluorescence intensity measurements of fluorescence-labeled anti-CD45 and anti-

CD16 to define granulocytic populations which include both neutrophils and eosinophils, in early maturation stages."

(Office Action, page 6)

The rejection is thus stated in broad generalities which are based upon the Examiner's interpretation of the cited references, not on specific disclosure, as these are then related to what is believed are the general parameters of Applicants claims, not the actual elements and limitations recited. When the cited references and their disclosures are considered in view of that which Applicants have specifically claimed, it becomes plain that the rejection is improper and should be withdrawn.

In generalizing the finding of obviousness as above, the Examiner makes no reference to the specific recitations in Applicants claims, nor are any citations to relevant locations in the cited references provided which are referenced to specific recitations in Applicants claims. Absent citation to specific disclosure related to specific claimed recitations, Applicants must ultimately guess at how the combination of citations are interpreted and used in the rejection, and how these render the claims obvious, if at all.

For instance, the Examiner maintains that step 5) is accounted for by the disclosure of Gopinath, and its apparent teaching with respect to using fluorescence intensity of fluorescent labeled anti-CD16 cell surface marker to identify eosinophils. Yet, the Examiner never adequately demonstrates how, particularly, this teaching meets each of the actual elements and limitations of Applicants claim 1, step 5). Applicants submit it does not.

Step 5) recites "distinguishing eosinophils and neutrophilic cells in the granulocytic cells obtained in step (4*) on the basis of the intensity of the fluorescence from* ***the first fluorescence-labeled antibody*** *and the intensity of the fluorescence from* ***the second or***

third fluorescence-labeled antibody." As Applicants have previously pointed out to the Examiner, Gopinath discloses a single step method for defining eosinophils using side scatter and fluorescence intensity of anti-CD116, and thus fails to disclose Applicants' particular distinguishing step involving three fluorescence-labeled antibodies recited in step 5). If the Examiner believes step 5) is specifically disclosed in Gopinath, Applicants respectfully request that the Examiner reference exactly where in Gopinath this may appear.

It is well settled that in order to establish a *prima facie* case of obviousness, each of the references cited must teach every element recited in the claims and identify the necessary motivation to combine these elements. *In re Rouffet,* 149 F. 3d 1350; 47 USPQ2d 1453 (Fed. Cir., 1998). If Gopinath does not provide the specific teaching or disclosure of the element(s) the Examiner admits to be lacking in Bowen then, *ipso facto*, and for this reason alone, the rejection must fail. Moreover, where neither Bowen nor Gopinath disclose step 5), it must follow that step 6) and step 7), which specifically perform actions on the cells and cell groups obtained in step 5), are also not disclosed or taught by the cited references.

Even though it fails to fill, at the very least, the Examiner's acknowledged gap in the disclosure of Bowen, the Examiner nonetheless relies on Gopinath for generally teaching the use of CD 16 in distinguishing between neutrophils and eosinophil populations. Given the Examiner's stated belief that Bowen "specifically taught" obtaining fluorescence intensity measurements of CD45 and CD16 in defining granulocytic populations, the Examiner considers that "combination of Bowen with Gopinath suggests step 5) of Claim 1." Applicant disagrees. As will be demonstrated, the Examiner's reading of Bowen and the asserted combination wholly lack the legal and factual groundings to support a *prima facie* case of obviousness.

For one, obviousness is determined based on whether the cited art contains a teaching or a suggestion that one should deviate from the disclosure of a reference, a teaching or suggestion which would have impelled one to do so, and to do what the Applicants have done. *Ex parte Markowitz*, 143 USPQ 303, 305 (Bd. App. 1964). Applicants respectfully submit that the proposed combination of Bowen and Gopinath lack any requisite suggestion to modify their respective and disclosed methods to arrive at what the Applicants have done. For these reasons alone, the rejection of the claims is insufficient and should be withdrawn. *Ex parte Levengood*, 28 USPQ2d 1300, 1301-02 (BPAI 1993).

In addition to the above legal deficiencies in the rejection, as asserted, the "specific" teaching which the Examiner references find no support in Bowen. Rather, granulocytic populations are defined in Bowen by measuring the fluorescence-labeled anti-CD45 and side scattered light (See Bowen, Fig. 1A and 1B on page 294), not by the fluorescence intensity measurements of fluorescent labeled anti-CD 45 and anti-CD 16. The scatterplots reproduced in Bowen illustrate measurements of Tri-Color CD 45 against log orthoganal light scatter. Others plot phycoerythrin CD 11b against flouroescein isothiocyanate conjugated CD 16. No figure plots fluorescence intensity measurements of fluorescent labeled anti-CD45 with respect to anti-CD 16, let alone to distinguish eosinophils.

Using Applicant's claim parlance solely to demonstrate flaws in the rationale supporting the rejection; were anti-CD 45 to be considered a "first" fluorescent labeled antibody (used in Bowen to define the granulocytic population by plotting it against scattered light), thereafter, as per Bowen, the fluorescent intensity of anti-CD 45 expression is not measured against a "second" or "third" fluorescent labeled antibody, and not used in any other respect to arrive at "distinguishing eosinophils and neutrophils" as Applicants have claimed.

Given this, the addition of Gopinath fails to bring Bowen any closer to meeting Applicants claims. Moreover, how the Examiner considers Gopinath to actually fit within the disclosure of Bowen, let alone how such combination or modification is motivated, taught or suggested, is even unclear. Apparently, the Examiner has not also resolved this in a manner logically consistent with the steps of claim 1, as recited. For example, the Examiner acknowledges Gopinath discloses a combination of side scatter and fluorescent intensity measurement of the fluorescent labeled anti-CD16 antibody to identify eosinophils, but still finds this to be a disclosure or teaching of Applicants' step 5) of claim 1 because "the current claim recitation does not exclude use of side angle scatter in making a distinction between eosinophils and other granulocytic populations."

Whether or not this is the case, however, it is extraneous to the consideration of all claimed elements and limitations and whether they are each taught or disclosed by the cited references. This, and not what the claims exclude, is what a *prima facie* case of obviousness demands. Whatever the claims may be thought to "exclude", the disclosure in Gopinath regarding the one step method using one fluorescent cell surface marker does not teach or disclose the elements and limitations recited step 5). Meanwhile Bowen fails to disclose a "first" fluorescence labeled antibody, the fluorescent intensity of which is used, along with the intensity of scattered light, to classify granulocytic cells and, along with a "second" or "third" fluorescent labeled antibody, used to distinguish eosinophils and neutrophilic cells. When this is compared to what the claims say, rather than what they do not say, there is no support for the rejection.

Facts and specifics drive the analysis of obviousness, not speculation or generalities. The rejection cannot be founded on elements not claimed, nor may the rationale supporting the rejection conflate the steps as recited to accommodate the citations, nor can it

contort and change the teachings and disclosures of the cited references to compensate for what is plainly lacking therein.. If resort to such generalizations is believed necessary to maintain the finding of obviousness, then the rejection is improper.

Based on the foregoing, Claim 1 is allowable over the cited art. As all other claims under rejection depend from Claim 1, with the exception of Claim 18, and therefore incorporate all claimed elements and limitations of Claim 1, these are also allowable. As to Claim 18, this claim includes all elements and limitations present in Claim 1, and hence, should also be deemed allowable.

In view of the above, reconsideration and withdrawal of this rejection is respectfully requested.

CONCLUSION

For the reasons set forth above, reconsideration, and allowance of the claims respectfully is requested. If the Examiner has any questions regarding this paper, please contact the undersigned attorney.

Respectfully submitted,

By: _____

Charles T. J. Weigell
Reg. No. 43,398
BRYAN CAVE LLP
245 Park Avenue
New York, NY 10167
Tel. No.: (212) 692-1898
Fax No.: (212) 692-1900

I hereby certify that this correspondence is being deposited with sufficient postage with the United States Postal Service as first class mail in an envelope addressed to the Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on November 5, 2004

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Charles T. J. Weigell